Genetic modeling of dizygotic twinning in pedigrees of spontaneous dizygotic twins

Meulemans, W.J.; Lewis, C.M.; Boomsma, D.I.; Derom, C.A.; Berghe, H.; Orlebeke, J.F.; Vlietinck, R.F.; Derom, R.M.

published in
American Journal of Medical Genetics
1996

DOI (link to publisher)
10.1002/(SICI)1096-8628(19960122)61:3<258::AID-AJMG10>3.0.CO;2-S

document version
Publisher's PDF, also known as Version of record

American Journal of Medical Genetics 61:258–263 (1996)

Genetic Modelling of Dizygotic Twinning in Pedigrees of Spontaneous Dizygotic Twins

Wim J. Meulemans, Cathryn M. Lewis, Dorret I. Boomsma, Catherine A. Derom, Herman Van den Berghe, Jakobus F. Orlebeke, Robert F. Vlietinck, and Robert M. Derom

Center for Human Genetics, Catholic University of Leuven, Leuven, Belgium (W.J.M., C.A.D., H.V.d.B., R.F.V., R.M.D.); Department of Medical Informatics, University of Utah, Salt Lake City, Utah (C.M.L.); and Department of Psychonomy, Free University of Amsterdam, Amsterdam, The Netherlands (D.I.B., J.F.O.)

The inheritance of spontaneous dizygotic (DZ) twinning was investigated in 1,422 three-generation pedigrees ascertained through mothers of spontaneous DZ proband twins. DZ twinning was modelled as a trait expressed only in women. The penetrance was modelled first as a parity independent and secondly as parity dependent. The observed frequencies of maternal and paternal grandmothers with DZ twins differed significantly from the expectations under an X-linked mode of inheritance. Complex segregation analysis showed that the parity-independent phenotype of "having DZ twins" was consistent with an autosomal monogenic dominant model, with a gene frequency of 0.035 and a female-specific lifetime penetrance of 0.10. Recessive, polygenic, and sporadic models were rejected. The autosomal dominant model revealed a strong robustness against a changing population prevalence and the loss of information due to the presence of same-sexed twin pairs of unknown zygosity. When DZ twinning was modelled as a parity dependent trait, the data were compatible with an autosomal dominant model with a gene frequency of 0.306 and a penetrance of 0.03 per birth for female gene carriers.

KEY WORDS: segregation analysis, pedigree analysis, dizygotic twinning

INTRODUCTION

The question of whether dizygotic (DZ) twinning is inherited is a century old. In 1902, Weinberg [1902] discovered higher DZ twinning frequencies among the offspring of female relatives of mothers of DZ twins. Wyshak and White [1965] observed DZ twinning rates of 1.45% for the offspring of a female DZ twin and of 1.65% for their female relatives. These frequencies exceeded the rate of 0.69% found among the offspring of male DZ twins. Bulmer [1970] showed that the relative risk of bearing DZ twins for daughters/mother and the sisters of women with DZ twins were 1.8 and 2.6 times higher than the general population, respectively. He postulated that a recessive gene with a low penetrance and a gene frequency of 50% caused the birth of spontaneous DZ twins. The underlying biological mechanism for DZ twinning is multiple ovulation [Milham, 1964]. Animal models have confirmed a genetic influence for multiple ovulation. Montgomery et al. [1993] localized an autosomal codominant gene (FecB) that increases the ovulation rate in Booroola sheep to a region homologous to human chromosome 4. The existence of an X-linked gene, which influences multiple ovulation and polyzygous multiple births, was demonstrated through segregation analysis in Romney sheep [Davis et al., 1991].

This study is the first to investigate the inheritance of DZ twinning by formal pedigree analysis. Complex segregation analysis, based upon the general model of Elston and Stewart [1971], was used to evaluate monogenic and mixed models as possible explanations for the familial occurrence of DZ twins. In contrast to other studies, the trait was defined as having DZ twins, not being a DZ twin. All analyses were limited to pedigrees of spontaneous DZ proband twins and the familial clustering of spontaneous DZ twins, i.e., DZ twins who were conceived without any prior use of ovulation inducing medication.

MATERIAL AND METHODS

Subjects

Spontaneous DZ proband twins were obtained through two population-based twin registers: the East Flanders Prospective Twin Study (EFPTS) [Vlietinck,

Received for publication August 2, 1994; revision received February 1, 1995.

Address reprint requests to Wim J. Meulemans, Center for Human Genetics, UZ Gasthuisberg O&N6, Catholic University of Leuven, Herestraat 49, 3000 Leuven, Belgium.

1986; Vlietinck et al., 1988] and The Netherlands Twin Register (NTR) [Boomsma et al., 1992]. Families of DZ proband twins, born in 1987 and 1988 in The Netherlands and between July 1, 1964, and September 30, 1990, in the province of East Flanders, Belgium, were mailed a questionnaire requesting family information. Pedigrees were constructed of the parents of the proband twins, the parents' siblings, their parents, and grandparents and included details of the offspring of these individuals. Responses were validated through civil birth registers and telephone calls or letters to the twin families. The zygosity of the spontaneous DZ proband twins was determined through gender, placental membranes, blood groups, and DNA typing [Vlietinck, 1986; Derom et al., 1985] in the EFPTS and through gender, blood groups, DNA typing [Jeffreys et al., 1985], and a similarity questionnaire in the NTR. The zygosity of additional twins in the families was determined by a similarity questionnaire administered by telephone or letter. The reliability of the similarity questionnaire was tested on a group of 329 same-sexed twin pairs (211 MZ, 118 DZ), whose zygosity had been confirmed through the aforementioned methods. Of all twin pairs, 96.7% were correctly classified by this similarity questionnaire.

Completed pedigrees were obtained from 1,422 of the 2,518 addressed families of DZ proband twins, giving a response rate of 56.5%. The representivity of the respondents in terms of familial twinning was evaluated by comparing them to a group of 70 non-respondent families, who were contacted by telephone. The same proportion of respondents and non-respondents reported additional twin pairs (599/1,422 versus 27/70, $P > 0.1$) and additional DZ twin pairs (414/1,422 versus 20/70, $P > 0.1$). Consequently, the group of 1,422 collaborating families was considered representative of all DZ twin families registered by either the NTR or the EFPTS in terms of familial DZ twinning.

Genetic Modelling

DZ twinning, defined as "having DZ twins," was modelled as a trait expressed only in women. The mother of the DZ proband pair therefore became the true proband. The original pedigree was restricted to the maternal family, consisting of the proband mother, her siblings, parents, and grandparents, and the information on the offspring of these individuals used to define their phenotype. Mothers were classified as affected or unaffected according to whether they did or did not have DZ twins. Males and women without offspring were categorized as having unknown phenotype. For some same-sexed twins, zygosity information was unavailable due to early death of one of the twins. Throughout this article, these twin pairs will be referred to as UZ twins. Summary statistics of the pedigrees were calculated under three different phenotype definitions, namely, with UZ twin mothers classified as unaffected, affected, and unknown.

An analysis of DZ twinning in the grandparental generation was used to compare X-linked and autosomal models. Under an autosomal model, a similar twinning rate should be observed among the maternal and paternal grandmothers of the proband mother. An X-linked gene is transmitted from father to proband mother with a probability of 1 and from mother to proband mother with a probability of 0.5. Consequently, under an X-linked model, twice as many paternal as maternal grandmothers should have spontaneous DZ twins. Chi-square tests were applied to compare the observed numbers of grandmothers with DZ twins to the expected numbers under autosomal and X-linked models.

In the segregation analysis, two different models for penetrance were used. Firstly, a parity independent penetrance gave each mother the same probability of bearing DZ twins, depending only on her genotype. Secondly, the penetrance was allowed to increase linearly by the mother's final parity up to a parity of 5, so that the penetrance for genotype G was Pen(G)*min(n, 5), where n is the final parity and Pen(G) is the penetrance for one birth for a woman of genotype G. This model would decrease the influence of women of low parity who had not given birth to DZ twins, and take some account of the decreasing sibship sizes observed in more recent generations of the pedigrees.

Complex segregation analysis of DZ twinning was carried out with the Pedigree Analysis Package (PAP) [Hasstedt and Cartwright, 1981], using an ascertainment correction for the original DZ proband mother [Cannings and Thompson, 1977]. Various autosomal models and the contribution of a polygenic component were tested. The hierarchically nested models were compared by the likelihood ratio test [Lehmann, 1986].

To ensure a valid model appropriate to the population, the gene frequency and penetrances were constrained so that the population prevalence of DZ twinning predicted under the genetic model was equal to the observed population prevalence. Under the assumption of a parity independent phenotype, the constraint was

$$p^2\text{Pen(AA)} + 2pq\text{Pen(AB)} + q^2\text{Pen(BB)} = \text{PP}$$

with p defined as the gene frequency of the affected allele A; q(= 1 − p) the frequency of the unaffected allele B; Pen(AA), Pen(AB), and Pen(BB) the penetrances of the genotypes AA, AB, and BB; and PP the population prevalence of DZ twinning. The population prevalence of DZ twin mothers was estimated at 0.71% using population statistics from The Netherlands of the parity dependent probabilities of a DZ twin birth and the distribution of family size. For the parity dependent phenotype where Pen(G) is a penetrance by birth, the population prevalence was divided by the mean parity observed in the pedigrees. The robustness of the best fitting model was measured by evaluating the impact of the population prevalence and the UZ twin mothers on the genetic modelling of DZ twinning.

RESULTS

Descriptive Epidemiology

A total of 1,422 maternal families of spontaneous DZ proband twins was obtained through the NTR and the EFPTS. The entire dataset contained 253 (4.4%) DZ

twin mothers out of a total of 5,731 non-proband mothers and 235 (16.5%) families with at least one additional DZ twin mother. In total 36/1,465 sisters, 76/1,422 mothers, and 75/1,422 maternal and 66/1,422 paternal grandmothers of the proband mother had spontaneous DZ twins. Given 151 affected grandmothers, under the assumption of an autosomal model, an equal number of affected maternal and paternal grandmothers would be expected (70.5). In case of an X-linked model, one would predict 47 maternal and 94 paternal grandmothers with DZ twins. The observed frequencies of affected maternal and paternal grandmothers were compatible with an autosomal ($P > 0.1$), but not with an X-linked model ($P < 0.001$).

UZ twins were observed among the offspring of 84 women. These UZ twins were not included in the previous phenotype definition and were in this way assumed to be monozygotic. To investigate the importance of these twins, the concept of DZ twinning was redefined as "having DZ or UZ twins," i.e., assuming all UZ to be DZ. The dataset contained 338 (5.9%) DZ and UZ twin mothers in 308 (21.7%) maternal families of spontaneous DZ proband twins. Expanding the phenotype definition by including UZ twin mothers caused a significant increase in the number of affected mothers ($P < 0.025$) and the number of families with additional affected mothers ($P < 0.0005$). In a third approach to the DZ twinning phenotype, UZ twin mothers were classified as unknown. This caused a decrease in the number of informative individuals, i.e., persons with a not-unknown phenotype, from 5,731 to 5,646 in the dataset. Consequently, the proportion of mothers of spontaneous DZ twins increased slightly, but not significantly, 253 (4.5%) DZ twin mothers were found in 235 (16.5%) families.

Genetic Analysis

Segregation analysis was initially carried out separately on the NTR and EFPTS. No heterogeneity was found between the datasets, and the results presented here are for the pooled families. Segregation analysis was first performed using the parity-independent phenotype definition. Results of the segregation analysis of the autosomal monogenic models are given in Table I. The recessive ($P < 0.0005$) and sporadic model ($P < 0.0005$) were rejected in favour of the dominant model ($P > 0.1$). The penetrance of the non-gene carriers in the dominant model converged at zero, the lower boundary. The penetrance of gene carriers in the dominant model was converged at 0.1025, and the gene frequency of 0.0352. Under a gene frequency of 0.0365 in the codominant model, the proportion of female homozygous carriers gave very little information to estimate the penetrance of this genotype. As a consequence, the parameter estimates in the codominant model were not significantly different from those of the best fitting dominant model. The polygenic model ($P < 0.0005$) was significantly rejected (Table II). In the mixed dominant model, the estimate of the polygenic heritability parameter was zero, indicating that no polygenic component was required in the genetic model.

The segregation analysis of autosomal monogenic models was performed on the same families as the parity dependent phenotype and results are presented in Table III. A sporadic ($P < 0.0005$) and recessive model ($P < 0.0005$) were significantly rejected. However, a dominant model ($P > 0.1$) was by parsimony favoured above the codominant model. Under this dominant model, female gene carriers would have a probability of 3.2% per birth to bear DZ twins. The penetrance of the female non-carriers converged at zero, implying no sporadic cases of DZ twins. The gene frequency was 0.036, very similar to the value from the parity independent modelling.

Model Diagnostics

The population prevalence of DZ twin mothers was estimated from Dutch population statistics to be 0.71%. The impact of the population prevalence on the autosomal monogenic modelling with parity independent penetrance was evaluated by comparing the models obtained at various levels of prevalence (Table IV). The autosomal dominant model fitted the data as well as its corresponding codominant model at each of the tested population prevalences. The recessive model was rejected at each prevalence value up to 0.025 with significance levels of $P < 0.0005$ up to 0.02 and $P < 0.01$ at 0.025 prevalence. Little discrimination was observed between the codominant, dominant, and recessive model at a prevalence of 0.03. The sporadic model was significantly rejected ($P < 0.0005$) at all prevalences. The gene frequency of the affected allele in the dominant model increased from 0.0044 at a population rate of 0.001 to 0.1857 at 0.03, while simultaneously a decrease in the penetrance of the gene carriers was observed from 0.1125 to 0.0799. At high prevalence values of 0.025 and 0.03, the penetrance of the non-carriers, Pen(BB), no longer maximized at the zero boundary,

TABLE I. Autosomal Monogenic Modelling of Dizygotic Twinning*

Model	Pen(AA)	Pen(AB)	Pen(BB)	Gene frequency	Degrees of freedom	−2 Ln likelihood
Codominant	0.2000 (0.0966)	0.0972 (0.0089)	0	0.0365	—	2,116.220
Dominant	**0.1025 (0.0071)**	**0.1025 (0.0071)**	**0**	**0.0352**	**1**	**2,117.200**
Recessive	0.1646 (0.0174)	0	0	0.2076	1	2,197.357
Sporadic	0.0071	0.0071	0.0071	—	3	2,581.762

*Pen(AA), Pen(AB), and Pen(BB) are the penetrances of the genotypes AA, AB, and BB and given together with the standard error on the estimate. Underlined parameters are fixed. Figures in bold represent the best fitting model. d.f. = degrees of freedom.

TABLE II. Mixed Modelling of Dizygotic Twinning*

Model	Polygenic heritability	Pen(AA)	Pen(AB)	Pen(BB)	Gene frequency	d.f.	−2 Ln likelihood
Mixed dominant	0	0.1025 (0.0071)	0.1025 (0.0071)	0	0.0352	1	2,117.200
Polygenic	0.7384 (0.0342)	0.0071	0.0071	0.0071	—	3	2,134.913
Dominant	**0**	**0.1025 (0.0071)**	**0.1025 (0.0071)**	**0**	**0.0352**	**2**	**2,117.200**

*Pen(AA), Pen(AB), and Pen(BB) are the penetrance coefficients of the genotypes AA, AB, and BB and given together with the standard error on the estimate. Underlined parameters are fixed. Figures in bold represent the best fitting model. d.f. = degrees of freedom.

but, respectively, at 0.0028 and 0.0098 for population frequencies 0.025 and 0.03.

Zygosity information was not available for 84 UZ twin pairs. To evaluate the influence of the UZ twin mothers on the genetic modelling of DZ twinning, segregation analysis was repeated, classifying mothers of UZ twins as unknown and as affected (Table V). The segregation analysis of DZ twinning when mothers of UZ twins were classified as unknown indicated a dominant mode of inheritance was the best fitting model ($P > 0.1$) and rejected the recessive ($P < 0.0005$) and the sporadic model ($P < 0.0005$). Autosomal monogenic modelling with UZ twin mothers categorized as affected, rejected the recessive ($P < 0.0005$) and sporadic models ($P < 0.0005$). The dominant model was by parsimony favoured above the codominant ($P > 0.1$). The penetrance of the carrier genotypes AA and AB in the dominant model increased to 0.1388 after extending the definition of DZ twinning to include UZ twins and the gene frequency decreased slightly to 0.0259. When mothers of UZ twins were classified as unknown, penetrance of gene carriers in the dominant model was estimated at 0.1039. This estimate was not significantly different from the value when mothers of UZ twins were categorized as unaffected. The gene frequency decreased only slightly to 0.0347. Penetrance of the non-gene carriers, BB, in the dominant model converged at zero under all three phenotype definitions.

DISCUSSION

Complex segregation analysis of DZ twinning, modelled as a parity-independent trait, indicated an autosomal dominant model as the best explanation for the familial clustering of DZ twins. The penetrance of carrier genotypes was estimated at 10.3% for female carriers, while the point estimate of the gene frequency was 3.5%. The penetrance of the non-gene carrier was zero, indicating that all DZ twin births were due to a genetic predisposition. The maximization of the polygenic heritability at zero clearly suggested the absence of a polygenic contribution in addition to the monogenic component of the model.

In a second approach, the penetrance became a function of both the genotype and the parity. The penetrance per birth was estimated per birth. An autosomal dominant mode of inheritance remained the best fitting model. For female gene carriers, the probability of giving birth to DZ twins was 3.2% per birth. The gene frequency was 0.0360. All cases of DZ twins were accounted for by this dominant gene as the penetrance estimate for non-carriers was zero. Given the average number of births per mother was 3.18, an average mother would have a penetrance of 10.2% under the parity-dependent model. This value was compatible with the penetrance of 10.3%, observed for female gene carriers in the dominant model under the assumption of a parity independent trait.

The strength of a model not only depends on its statistical difference with other competitive models, but also on the assumptions made in developing the model. Two different aspects of our analysis were evaluated: population prevalence and zygosity determination. Analysis showed that the dominant model with low penetrance and no sporadic cases was robust to changes in these factors. The gene frequency was constrained through the penetrances to ensure that the predicted population prevalence under the genetic model would match the observed population frequency of mothers of DZ twins, namely 0.71%. The autosomal dominant monogenic model remained the best fitting with increasing population prevalence. Statistical discrimination between the dominant and recessive models only decreased at values of 2.5 and above, but these are not plausible values for the population prevalence of DZ twinning.

To investigate the importance of the UZ twin mothers on the genetic modelling of DZ twinning, the segregation analysis was repeated with UZ twin mothers clas-

TABLE III. Parity Dependent Autosomal Monogenic Modelling of Dizygotic Twinning*

Model	Pen(AA)	Pen(AB)	Pen(BB)	Gene frequency	Degrees of freedom	−2 Ln likelihood
Codominant	0.0636 (0.0382)	0.0298 (0.0031)	0	0.0373	—	2,042.041
Dominant	**0.0316 (0.0022)**	**0.0316 (0.0022)**	**0**	**0.0360**	**1**	**2,042.700**
Recessive	0.0622 (0.0068)	0	0	0.1895	1	2,094.147
Sporadic	0.0071	0.0071	0.0071	—	3	2,502.042

*Pen(AA), Pen(AB), and Pen(BB) are the penetrances of the genotypes AA, AB, and BB and given together with the standard error on the estimate. Underlined parameters are fixed. Figures in bold represent the best fitting model. d.f. = degrees of freedom.

TABLE IV. Comparison of Autosomal Monogenic Models as a Function of the Population Prevalence of Dizygotic Twinning*

Population prevalence	Dominant (1 d.f.)		Recessive (1 d.f.)		Sporadic (3 d.f.)	
	χ^2	P	χ^2	P	χ^2	P
0.001	2.68	0.15	329.48	0.0005	1361.8	0.0005
0.005	1.14	0.30	115.12	0.0005	613.5	0.0005
0.010	0.88	0.40	53.28	0.0005	330.9	0.0005
0.015	0.86	0.40	27.86	0.0005	190.3	0.0005
0.020	0.93	0.40	14.52	0.0005	107.7	0.0005
0.025	1.00	0.40	7.18	0.01	56.6	0.0005
0.030	1.18	0.20	3.06	0.1	25.5	0.0005

*d.f. = degrees of freedom. The difference in likelihood with the codominant model is expressed as a χ^2 value and given together with the number of degrees of freedom and the P-value.

sified as unknown and affected. The pedigrees had 253 non-proband mothers of DZ twins, and 84 mothers of UZ twins. Despite the high numbers of women involved in the phenotype changes, little effect was seen on the results of the segregation analysis. Predictably, the inclusion of mothers of UZ twins as affected increased the penetrance of the trait but the dominant model remained the best fitting model.

The phenotype of DZ twinning used in this study had a low penetrance of 3.2% per birth. DZ twinning is easily measured but is an incomplete surrogate for multiple ovulation, which is the primary trait of interest. Multiple ovulation may not result in the birth of DZ twins, through lack of fertilization, spontaneous abortions, or fetal death. The low penetrance of 10% for mothers of DZ twins may well be higher if multiple ovulation is measured. Martin et al. [1991] showed that mothers of DZ twins had significantly higher follicular activity compared to controls. Leridon [1977] estimated that 42% of all conceptions survive to a clinical identified pregnancy. If two fertilized eggs had the same chance of surviving, this would mean that approximately 17.6% (the square of 42%) of all multiple conceptions would be recognized as a multiple pregnancy. Boklage [1990] estimated that although multiple pregnancies represent about 12% of all natural conceptions, only 2% of all multiple conceptions will survive to term as twins and about 12% end with the birth of a singleton.

Using the parity independent dominant genetic model, the risk ratio for female first degree relatives of mothers of DZ twins was calculated to be 7.5. Most other studies of the familiality of DZ twinning have estimated relative risks using the total number of DZ twin and singleton births in the relatives of mothers of DZ twins. Bulmer [1970] pooled data from several studies to obtain a risk ratio of 2.6 for sister of mothers of DZ twins, compared to the general population. This figure is a risk per birth, and so a lifetime figure would be similar to the risk to first degree relatives obtained in this pedigree study.

Modelling with DZ twinning is fraught with problems in the choice of phenotype and risk factors to include. In this study, we have chosen to the model the phenotype of "having DZ twins" as opposed to "being a DZ twin," and have included DZ and UZ twins, but not MZ twins. This phenotype definition enables us to compare results of other studies of the familiality of DZ twinning, and is a clear outcome of multiple ovulation. At a population level, known risk factors for the birth of DZ twins are maternal age and parity [Bulmer, 1970]. No genetically susceptible subset of women has been identified through these parameters. For example, Lewis et al. [1995] found that maternal age at birth of DZ twins was independent of a family history of DZ twinning. Two parameters were modelled in this study: population frequency and mother's parity. Parity here represents the number of opportunities a woman has had to express that trait of DZ twinning, and is key to consider, although the dominant model remained the best fitting when parity was excluded.

The results that DZ twinning is inherited as a dominant model contradicted the recessive model previously

TABLE V. Monogenic Autosomal Modelling of Dizygotic Twinning Under Different Definitions of Dizygotic Twinning*

Phenotype definition	Model	Pen(AA)	Pen(AB)	Pen(BB)	Gene frequency	d.f.	−2 Ln likelihood
UZ twin mothers are unknown	Codominant	0.2014 (0.0982)	0.0988 (0.0090)	0	0.0359	—	2,109.685
	Dominant	**0.1039 (0.0072)**	**0.1039 (0.0072)**	**0**	**0.0347**	**1**	**2,110.668**
	Recessive	0.1665 (0.0175)	0	0	0.2064	1	2,192.818
	Sporadic	0.0071	0.0071	0.0071	—	3	2,580.551
UZ twin mothers are affected	Codominant	0.3291 (0.1258)	0.1341 (0.0096)	0	0.0268	—	2,656.408
	Dominant	**0.1388 (0.0081)**	**0.1388 (0.0081)**	**0**	**0.0259**	**1**	**2,658.639**
	Recessive	0.2349 (0.0207)	0	0	0.1738	1	2,807.171
	Sporadic	0.0071	0.0071	0.0071	—	3	3,421.725

*P(AA), P(AB), and P(BB) are the penetrance coefficients of the genotypes AA, AB, and BB and given together with standard error on the estimate. Underlined parameters are fixed. Figures in bold represent the best fitting model. d.f. = degrees of freedom; UZ = same-sexed pairs of unknown zygosity.

suggested [Bulmer, 1970] from studies which did not use pedigree analysis. The large set of families used and the robustness of the dominant model to changes in the definitions of phenotype definition, penetrance, and population prevalence give confidence in these results, although not all factors relevant for DZ twinning have been included. The dominant model would be compatible with the autosomal codominant gene for multiple ovulation in Booroola merino sheep [Montgomery et al., 1993]. In humans, the trait of DZ twinning is an incomplete surrogate for multiple ovulation and clearly has low penetrance, even in genetically predisposed women. This study showed that DZ twinning is sufficiently informative for genetic analyses and the evidence for a dominant mode of inheritance should lead to further studies into genetic predisposition for DZ twinning and multiple ovulation.

ACKNOWLEDGMENTS

This work was supported by grants 3.0038.82 and 3.0008.90 of the Fund for Medical Scientific Research (Belgium), grant 002818470 of the Praeventiefonds (The Netherlands), and NATO grant 860823. The authors gratefully acknowledge the help of Mrs. C. van Baal, T. Stroet, and P. Grootveld in The Netherlands and Mrs. D. Celen, F. Cormenier, V. De Witte, V. Bekaert, C. Ponnet, and W. Bosman in Belgium, who were all actively involved in the data collection. We thank Dr. Nick Martin for useful discussions throughout this work.

REFERENCES

Boklage CE (1990): Survival probability of human conceptions from fertilization to term. Int J Fertil 35:75–84.

Boomsma DI, Orlebeke JF, van Baal GCM (1992): The Dutch Twin Register: Growth data on weight and height. Behav Genet 22: 247–251.

Bulmer MG (1970): "The Biology of Twinning in Man." London: Oxford University Press, pp 113–137.

Cannings C, Thompson EA (1977): Ascertainment in the sequential sampling of pedigrees. Clin Genet 12:208–212.

Davis GH, McEwan JC, Fennessy PF, Dodds KG, Farquhar PA (1991): Evidence for the presence of a major gene influencing ovulation rate on the X chromosome of sheep. Biol Reprod 44:620–624.

Derom C, Bakker E, Vlietinck R, Derom R, Van Den Berghe H, Thiery M, Pearson P (1985): Zygosity determination in newborn twins using DNA variants. J Med Genet 22:279–282.

Elston RC, Stewart J (1971): A general model for the genetic analysis of pedigree data. Hum Hered 21:523–542.

Hasstedt SJ, Cartwright PE (1981): PAP: Pedigree analysis package. Tech rep 13. Department of Medical Biophysics and Computing, University of Utah, Salt Lake City.

Jeffreys AJ, Wilson V, Thein SL (1985): Hypervariable "minisatellite" regions in human DNA. Nature 314:67–73.

Lehmann EL (1986): "Testing Statistical Hypothesis." New York: John Wiley.

Leridon H (1977): "Human Fertility: The Basic Components." Chicago: University of Chicago Press.

Lewis CM, Healey S, Martin NG (1995): Genetic contribution to DZ twinning. Am J Med Genet 61:237–246.

Martin NG, Robertson DM, Chenevix-Trench G, de Kretser DM, Osborne J, Burger HG (1991): Elevation of follicular phase inhibin and luteinizing hormone levels in mothers of dizygotic twins suggests nonovarian control in humans. Fertil Steril 56:469–474.

Milham S (1964): Pituitary gonadotrophin and dizygotic twinning. Lancet ii:566.

Montgomery GW, Crawford AM, Penty JM, Dodds KG, Ede AJ, Henry HM, Pierson CA, Lord EA, Galloway SM, Schmack AE, Sise AE, Swarbrick PA, Hanrahan V, Buchanan FC, Hill DF (1993): The ovine Booroola fecundity gene (FecB) is linked to markers from a region of human chromosome 4q. Nature Genet 4:410–414.

Vlietinck R (1986): "The Determination of Zygosity of Twins." Katholieke Universiteit Leuven. Leuven: PhD thesis.

Vlietinck R, Papiernik E, Derom C, Grandjean H, Thiery M, Derom R (1988): The European multiple birth study (EMBS). Acta Genet Med Gemellol 37:27–30.

Weinberg W (1902): Beitrage zur Physiologie und Pathologie der Mehrlingsgeburten beim Menschen. Pflugers Arch 88:346–430.

Wyshak G, White C (1965): Genealogical study of human twinning. Am J Public Health 55:1586–1593.